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REVIEW

The potential role of intracavernosal injection of platelet-rich plasma for treating patients with mild to moderate erectile dysfunction: A GRADE-Assessed systematic review and meta-analysis of randomized controlled trials

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Summary ***Introduction: Platelet-rich plasma (PRP) has shown positive effects on enhancing erectile function in animal studies. Human clinical trials are limited and provide contradictory results. This review aims to conduct a meta-analysis of the available Randomized controlled trials (RCT) to assess the efficacy of PRP in males with ED.***
Methods: A systematic review was carried out following the Cochrane Handbook of Intervention and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and registered in PROSPERO (CRD42023441655).
Results: A total of three RCTs were included in the analysis for a total of 221 patients with mild to moderate ED. The patients receiving PRP reported significantly better improvement of IIEF-EF score during 1,3- and 6-months follow-up compared to the placebo group (mean difference [MD] 2.66, 95% confidence interval [CI] 1.48 to 3.83, p < 0.01; MD 2.11, 95%CI 0.13 to 4.09, p = 0.04; MD 2.99, 95%CI 1.79 to 4.19, p < 0.01). The pooled analysis indicated that attainment of minimally clinical important difference (MCID) was significantly higher in patients receiving PRP compared to the placebo group during one and 6-month follow-up (odds ratio [OR] 5.51, 95%CI 1.2 to 254, p = 0.03; OR 5.64, 95%CI 2.05 to 15.55, p < 0.01; respectively). Encouragingly, no major AEs were reported in all three trials in the PRP and placebo groups (p = 0.99).
Conclusions: This review highlights the potential role of PRP in providing short-term improvement of erectile function parameters for up to 6 months in mild to moderate ED patients. Future RCTs with longer-duration follow-ups and more standardized treatment protocols are necessary to gain sufficient details on PRP's long-term effectiveness and safety.

KEY WORDS: Platelet-rich plasma; Erectile dysfunction; Regenerative medicine; Sexual and reproductive health; Reproductive health.

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INTRODUCTION

Erectile dysfunction (ED) is one of the most common male sexual dysfunctions globally (1). This condition not only impairs the patient's quality of life, but it also has a detrimental impact on their partners (2). Treatment of ED is tailored to its underlying etiology, which is highly individualized, ranging from conservative, medicinal, and surgical approaches (3). Conservative approaches, such as lifestyle adjustments and risk factor management, can be advised for individuals with mild ED; however, patients with symptomatic ED may require medical or even surgical therapeutic approaches (4). Several treatments are available to control the symptoms, including PDE5i, topical vasoactive therapy, and a vacuum erection device (5). Nevertheless, studies reveal that the majority of ED patients have poor compliance; data suggest that one out of four patients will discontinue pharmacological therapy, with one of the most common reasons is the unwillingness to depend on pharmacological medicine and the desire for natural, spontaneous erections (6). Therefore, the ability to achieve a natural spontaneous erection is one of utmost importance in patients with ED. The main problem with the earlier ED treatment paradigm is that it focuses on alleviating symptoms rather than restoring natural erectile function or halting disease progression. Accordingly, researchers worked on discovering alternate treatments that might naturally improve erectile function (7). Recently, a group of treatments known as regenerative medicine aim to restore the structure and function of erectile tissues, such as *Low-intensity shockwave therapy* (LISWT), stem cell therapy, and *platelet-rich plasma* (PRP) (7-9). PRP, a novel regenerative therapy with high rejuvenating potential and minimal side effects, contains various platelet growth factors produced from whole blood, such as *fibroblast growth factor* (FGF), *platelet-derived growth factor* (PDGF), and *vascular endothelial growth factor* (VEGF), which can heal injured penile tissue and restore erectile function (10, 11). In animal studies, researchers discovered that PRP can successfully enhance natural erectile function (12-14). Human clinical trials, on the other hand, remain scarce and conflicting (15-17). Therefore, the aim of this study is to conduct a meta-analysis of the available *Randomized controlled trials* (RCT) to assess the efficacy of PRP in males with ED.

Material and methods

Study protocol and search strategy

The search was carried out with several online databases such as *PubMed*, *Scopus*, and *ScienceDirect*, utilizing *Medical Subject Headings* (MeSH®) terms relevant to platelet-rich plasma and erectile dysfunction for publications published up to July 2023 following the Cochrane Handbook of Intervention and the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) (18, 19). The detailed review protocols were available in PROSPERO (CRD42023441655).

Article eligibility criteria

The inclusion criteria were sexually active men diagnosed with *erectile dysfunction* (ED) according to the *International Index of Erectile Function* (IIEF) score, receiving the intervention of intracarvernosal injection of PRP, compared to the intervention of placebo, reporting one of the following the outcomes, *minimal clinically important difference* (MCID), change of *International Index of Erectile Function-Erectile Function* (IIEF-EF) from baseline, *Sexual Encounter Profile question 3* (SEP-3), *peak systolic velocity* (PSV), *end-diastolic velocity* (EDV), minor adverse events, and major adverse events. All studies without full-text and non-English were excluded.

Data collection and quality assessment

To ensure accuracy in collecting baseline characteristics for the study, two independent authors used a piloted data collection sheet. Any discrepancies were resolved through discussion involving a third author. Collected data included patients' baseline characteristics, such as study location, study design, number of participants, age, follow-up period, and the first author's name. Data gathering was done using *Microsoft Excel® 2021*. The *Cochrane Risk of Bias* (RoB) Tool 2 was utilized to assess the bias risk of the RCTs included in the study (20).

Data synthesis and presentation

The effect size estimates of the meta-analysis were displayed as *odds ratio* (OR) and *mean difference* (MD) with 95% *confidence interval* (95% CI) for binary and continuous outcomes, respectively. Where the data from trials were presented as median and range, the mean and *standard deviation* (SD) were computed using *Wan et al.*'s formula (21). When a study did not provide sufficient information on the change in SD, we calculated data imputation using the formula for imputing SD from the baseline (18). The model used for analysis was selected based on the heterogeneity of the included study. We used the I^2 index and heterogeneity χ^2 test to evaluate heterogeneity between the studies The study being analysed had considerable heterogeneity, as indicated by $I^2 > 50\%$ and heterogeneity p-value < 0.05. Therefore, the random-effects *DerSimonian and Laird Model* was chosen for the analysis. If the heterogeneity was not significant, the fixed-effects model would have been used instead (3).

In this study, we considered a p-value < 0.05 statistically significant. To evaluate the certainty of evidence, the *Grading of Recommendations, Assessment, Development, and Evaluations* (GRADE) method was employed using GRADEpro GDT (22). All statistical analyses were performed using *STATA® 16*.

Results

Baseline characteristics and risk of bias of the included trials

The initial database search revealed 1.050 abstracts related to the use of PRP in ED patients. Thirteen studies were extracted for full-text eligibility assessment after screening the abstract using the pre-defined eligibility criteria. Finally, three double-blinded RCTs were included in the review as

Figure 1.
PRISMA flow diagram 2020.

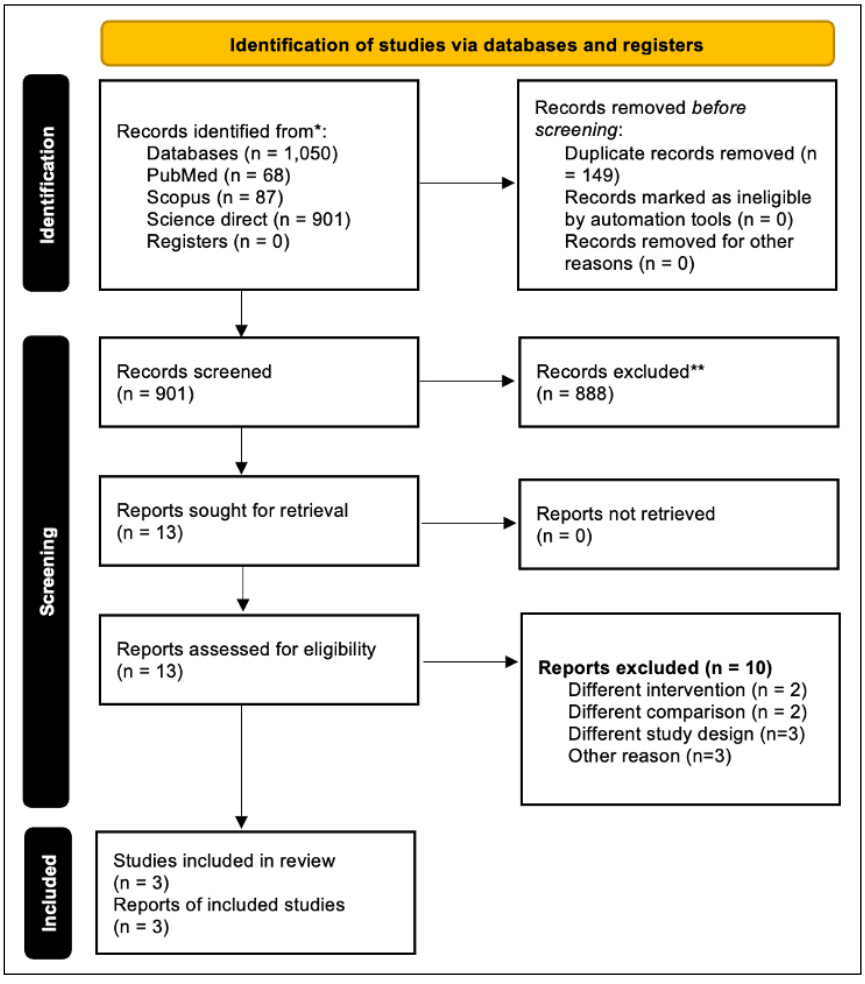

Table 1.
Baseline characteristics of the included studies.

Author	Country	Study design (LoE)	Trial ID	Group	Participant (n)	Participant analyzed (n)	Excluded from final analysis	Mean Age (yr)	BMI (kg/m^2)	Smoker (%)	HT) (%	DM (%)	Baseline IIEF	ED Severity		
														Mild	Mild-moderate	Moderate
Poulios, et al. 2021	Greece, Europe	Double-blinded RCT (1B)	NCT 04050020	PRP group	30	29	3%	58	29.4	53	33	37	20.4	43%	47%	10%
				Placebo group	30	26	12%	59	28.5	63	27	13	19.4	23%	60%	17%
Shaher, et al. 2023	Egpyt, Africa	Double-blinded RCT (1B)	Not reported	PRP group	55	50	10%	56	25	54	36	30	18	30%	50%	20%
				Placebo group	54	50	8%	54	24.9	56	28	34	19	26%	56%	18%
Masterson, et al. 2023	Florida, America	Double-blinded RCT (1B)	NCT 04396795	PRP group	28	20	29%	49	27.9	92	28.6	10.7	17.4	57%	-	43%
				Placebo group	33	24	28%	46	28.5	100	30.3	9.1	18.6	63%	-	36%

displayed in Figure 1. Table 1 represents the baseline characteristics of the participants of the included trials. Trials were conducted on several continents with similar ages and nutritional statuses. The majority of the participants were classified with mild and mild-moderate ED.

Figure 2 displays the summary of the risk of bias Assessment by evaluating the five domains. There were some concerns regarding bias arising from the randomization process in the Trial by *Poulios et al.*, as there were insufficient details regarding the randomization methods (17). The trial by *Masterson et al.* showed some concerns in terms of bias due to missing outcome data, as the trial reported a high rate of patients excluded from analysis (16). However, the analysis summary demonstrated an overall low risk of bias among the included trials.

Treatment protocols and outcomes of the included trials

Table 2 provides detailed information regarding the trial protocol and outcomes. The percentage rate of participants excluded from the final analysis ranged from 3% to 29% due to loss of follow-up or missing outcome data. All included trials take the PRP sample from the patient's autologous blood samples, with 2-3 injection sites sepa-

Figure 2.
Risk of bias assessed using RoB2 by Cochrane.

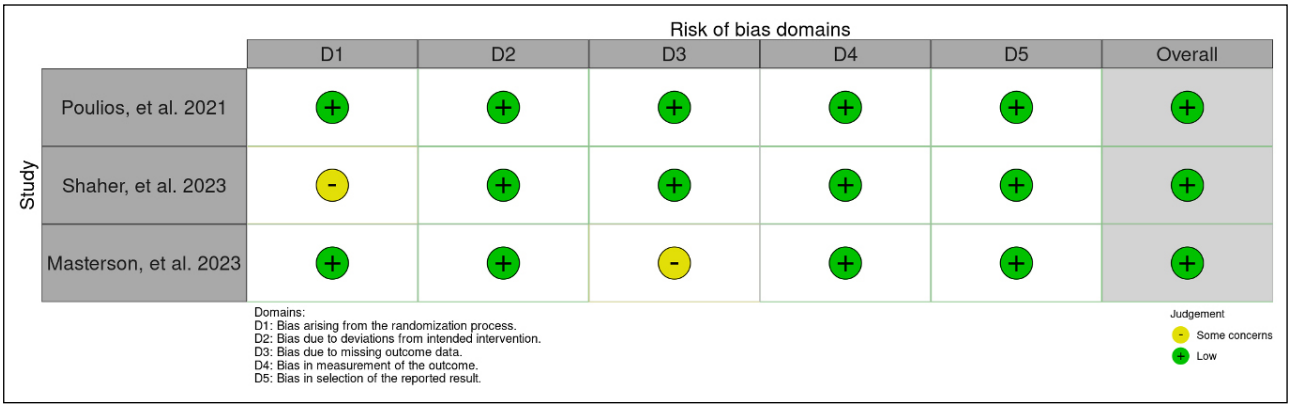

Table 2.
Treatment protocols and outcomes of the trials.

Author	Group	Inclusion criteria	Exclusion criteria	PRP source	Treatment protocol	Total session	Follow-up	Final mean IIEF change	Final SEP-3 Change (%)	Adverse effects	Pain scale (1-10)
Poulios, et al. 2021	PRP group	- Sexually active male aged 40-70 yo - Mild- moderate ED - ED treatment cessation	- Major pelvic surgery/trauma - Anatomical disorder affecting erectile function - Abnormal testosterone level - Psychogenic ED	60 mL autologous blood	5 ml of PRP, 2 sites of injection	2 session, 1 mo interval	6 month	3.3	20	None	2.6
	Placebo group				5 ml of saline, 2 sites of injection	2 session, 14 d interval		-0.2	-9		2.2
Shaher, et al. 2023	PRP group	- Sexually active male aged 45-60 yo - Mild- moderate ED - ED treatment cessation	- Major pelvic surgery - Abnormal testosterone level - Psychogenic ED	30 mL autologous blood	3 ml of PRP, 3 sites of injection	2 session, 14 d interval	6 month	2.6	66	None	1.52
	Placebo group				3 ml of saline, 3 sites of injection	2 session, 28 d interval		0	0		1.54
Masterson, et al. 2023	PRP group	- Sexually active male aged 30-75 yo - Mild- moderate ED - PDE5i treatment continued	- Urological surgery - Abnormal testosterone level - Psychogenic ED - Abnormal HbA1c level	120 mL autologous blood	2.5 ml PRP, 2 sites of injection	2 session, 28 d interval	6 month	5	Not reported	1 Penile plaque (3.5%) 1 Penile hematoma (3%)	3.7
	Placebo group				2.5 ml saline, 2 sites of injection	2 session, 28 d interval		2.2	Not reported		3.5

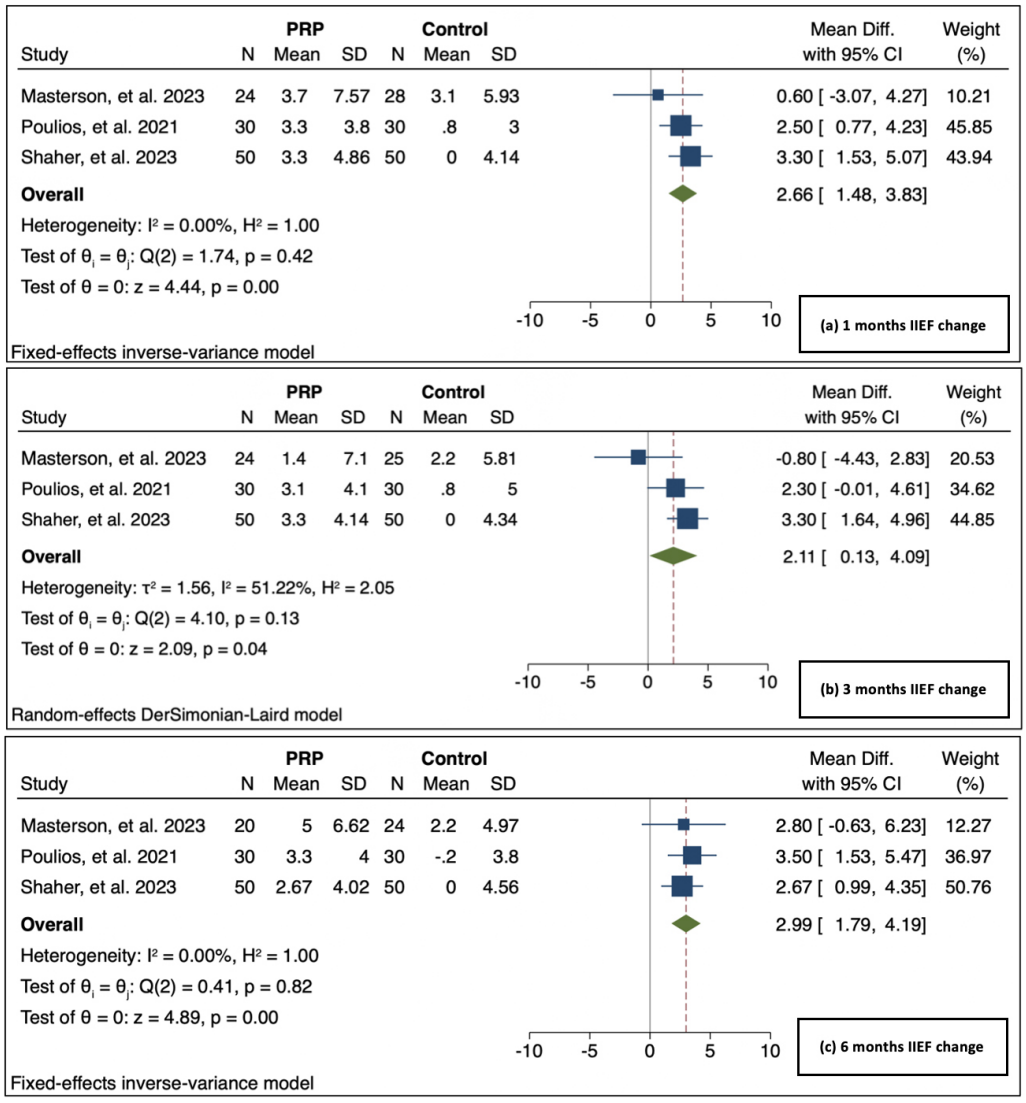

Figure 3.
Change of IIEF-EF score in (a) 1 month, (b) 3 month, and (c) 6 months between ED patients receiving PRP and placebo.

rated in 2 sessions at 2-week- to 4-week intervals. All of the included trials demonstrated higher IIEF change in the PRP group compared to the placebo group, with the most remarkable change of IIEF from baseline reported by *Poulios et al.* with the adjusted mean difference of 3.9 (1.8, 5.9, $p < 0.01$) (17). In terms of *minimally clinical important difference* (MCID), earlier trials by *Poulious et al.* and *Shaher et al.* reported that PRP had a higher attainment of MCID compared to placebo (69% *vs* 27%, $p < 0.01$; 70% *vs* 16%, $p < 0.01$; respectively), with the exception of an insignificant difference by *Masterson et al.* (60% *vs* 41.7%, $p = 0.226$) (16).

After six months of follow-up, trials showed no major or minor adverse effects, except for penile plaque in one of the PRP groups and hematoma in one of the placebo groups in the trial by *Masterson et al.* (16).

Results from pooled analysis

The meta-analyses were conducted from three trials for a total of 221 patients with mild to moderate ED. Figure 3 displays the pooled analysis of patients receiving PRP, which demonstrates significantly better improvement of IIEF-EF score during 1,3- and 6-months follow-up compared to the placebo group (MD2.66, 95% 1.48 to 3.83, $p < 0.01$; MD 2.11, 95%CI 0.13 to 4.09, $p = 0.04$; MD 2.99, 95% CI 1.79 to 4.19, $p < 0.01$, respectively). The pooled analysis indicated that attainment of MCID was significantly higher in patients receiving PRP compared to the placebo group during one and 6-month follow-up [*odds ratio* (OR) 5.51, 95%CI 1.2 to 254, $p = 0.03$; OR 5.64, 95%CI 2.05 to 15.55, $p < 0.01$; respectively], as displayed in Figure 4. Encouragingly, there were no major AEs reported in all 3 trials in the PRP and placebo groups ($p = 0.99$).

Results from the assessment of certainty of evidence

Table 3 provides detailed information regarding the assessment of certainty evidence. The evidence certainty indicated that the change in IIEF-EF from one to six months follow-up had a moderate level of certainty, with no serious problems regarding inconsistency, imprecision, or other factors. The analysis of MCID change revealed low certainty of evidence due to considerable imprecision concerns arising from the wide range of confidence intervals. The rating was downgraded due to significant heterogeneity in the included trials, but upgraded because of its large effects size (23).

Table 3.
Summary of certainty of evidence evaluated using GRADE approach.

Outcome	Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Overall certainty Oof evidence	PRP	Placebo	Anticipated effects
1 month IIEF change	212 (3 RCTs)	not serious [a]	not serious	serious [c]	not serious	none [e]	⊕⊕⊕◯ Moderate	104	108	MD 2.66 (1.48, 3.83)
3 month IIEF change	209 (3 RCTs)	not serious [a]	not serious	serious [c]	not serious	none [e]	⊕⊕⊕◯ Moderate	105	104	MD 2.11 (0.13, 4.09)
6 month IIEF change	204 (3 RCTs)	not serious [a]	not serious	serious [c]	not serious	none [e]	⊕⊕⊕◯ Moderate	104	100	MD 2.99 (1.79, 4.19)
1 month MCID	209 (3 RCTs)	not serious [a]	serious [b]	serious [c]	serious [d]	strong association [e]	⊕⊕◯◯ Low	74/103 (71.8%)	31/106 (29.2%)	OR 5.52 (1.20, 25.40)
3 month MCID	204 (3 RCTs)	not serious [a]	serious [b]	serious [c]	serious [d]	strong association [e]	⊕⊕◯◯ Low	66/101 (65.3%)	31/103 (30.1%)	OR 3.22 (0.57, 18.25)
6 month MCID	199 (3 RCTs)	not serious [a]	serious [b]	serious [c]	serious [d]	strong association [e]	⊕⊕◯◯ Low	67/99 (67.7%)	25/100 (25.0%)	OR 5.64 (2.05, 15.55)

[a] *Low risk of bias according to the assessment of RoB 2;*
[b] *Downgraded because high heterogeneity in the included trials evaluated by I^2 index;*
[c] *Downgraded because the included trials restricted to patient with mild-moderate erectile dysfunction with heterogeneous treatment protocols;*
[d] *Downgraded because the included trials demonstrated a wide range of confidence intervals;*
[e] *Upgraded because of the effect is large.*

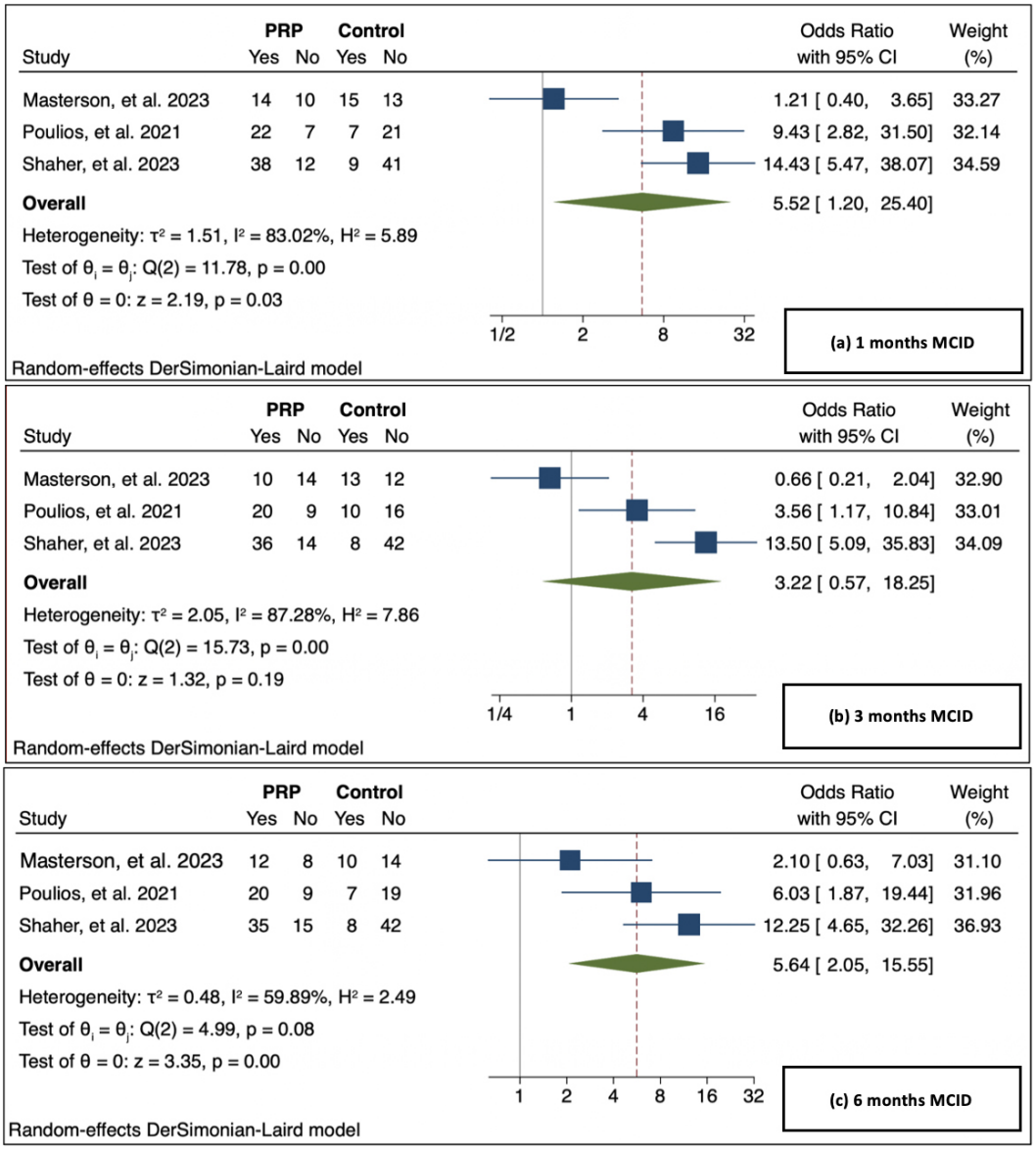

Figure 4.
MCID in (a) 1 month, (b) 3 month, and (c) 6 months between ED patients receiving PRP and placebo.

Discussion

Recent developments in the field of erectile dysfunction therapy have undergone a paradigm shift, moving beyond the mere treatment of symptoms to address the underlying pathology through regenerative medicine (24). Earlier reviews have previously highlighted the potential benefits of integrating regenerative medicine in improving erectile function, with the majority emphasizing shockwave therapy (25-28). The evidence regarding regenerative medicine is growing and even the EAU guideline is now recommending it as part of treatment for selected ED patients (7, 29, 30).

The findings of our review provided an additional interesting new insight into PRP as a novel regenerative therapy for ED. PRP's use in medical therapy has been grown since its inception in the recent decades, with reports of use in orthopedics, neurology, dermatology, cardiothoracic surgery, and now urology (31-34). Although the use of PRP in urology is still in its infancy, several animal trials and observational studies have demonstrated the benefits in patients with bladder dysfunction, bladder pain syndrome, cystitis, Peyronie's disease, and ED (13, 35, 36).

To determine the role of PRP in patients with ED, several outcomes are evaluated. One of the most important endpoints to consider is the IIEF-EF score. The EF domain included specific questions about erection frequency, erection firmness, penetration ability, maintenance frequency, maintenance ability, and erection confidence that were intended to determine the severity of ED (37). The improvement of IIEF-EF score reflects the benefits of the treatment for ED patients. The significance of PRP in improving IIEF-EF score was first demonstrated in a placebo-controlled trial by *Poulios et al.* which found an adjusted mean difference of 3.9 points compared to the placebo group during the six-month follow-up (17). This evidence is further supported by a recent trial by *Shaher et al.* which showed a significantly higher IIEF-EF in the PRP group (15). In contrast, the latest RCT in the American population showed an insignificant difference in IIEF-EF score between the PRP and placebo groups. In this review, we discovered that in six month follow-up, PRP significantly improve IIEF-EF score compared to placebo, with a mean difference of 2.99 points. When we look solely at the aggregate mean difference on the pooled analysis between PRP and placebo, the difference is relatively minor and it might be clinically irrelevant.

In order to objectively measure the clinical relevance of PRP for treating ED, we analysed the attainment of MCID, an endpoint to determine the minimum amount of objective change required in the EF domain to be meaningful to patients (38, 39). Prior trials by *Poulios et al.* and *Shaher et al.* found that patients who received PRP obtained a greater MCID at the final follow-up compared to those who received placebos (15, 17). However, the latest trial by *Masterson et al*. observed a slightly higher but statistically insignificant difference in MCID (16). When the evidence was pooled, the analysis revealed a significantly greater attainment of MCID in PRP during the final follow-up, with an OR of 5.64 times compared to placebo. Previous studies have also demonstrated significant improvements in other patient-reported outcome measures, including SEP-2 and SEP-3 in the PRP group. However, due to limited data, a meta-analysis could not be performed.

Several trials evaluated objective parameters, including penile vascular parameters. In *Shaher et al.*'s trial, notable enhancements were observed in peak systolic velocity and end diastolic velocity (15). However, the most recent trial by *Masterson et al.* found no meaningful differences (16). Insufficient data makes it impossible to conduct a meta-analysis, and a definitive conclusion on alterations in penile vascularity cannot be drawn from the existing evidence.

Regarding safety, extant trials have reported minimal to no side effects of PRP in patients with ED during short-term follow-up. Notably, *Masterson et al.* reported a single minor side effect in both treatment groups, with no major side effects observed during the trial (16). Our review of the literature demonstrates that pooled analyses revealed insignificant differences in side effects between PRP and placebo arms. It is important to note, however, that available studies only reported a limited period of follow-up, and the long-term safety of PRP in ED patients has yet to be well-established.

All trials uniformly applied specified exclusion criteria, which was participants with anatomical, hormonal, and psychogenic causes of erectile dysfunction. The observed difference in the included trial might be attributable to the heterogeneity of treatment protocols. For example, the trial by *Masterson et al.* used two sessions of a total of 5 ml of PRP concentrated from 120 ml of autologous blood (16). On the other hand, *Poulios et al.* used two sessions with a total of 10 ml of PRP concentrated from 60 mL of autologous blood (17). According to earlier studies, several factors, including overall platelet concentration, leucocyte and hemoglobin concentrations, the technique of activation of PRP, and *mean-platelet volume* (MPV) level, could affect the bioavailability of growth factors and play a role in determining the success rate of PRP in ED patient (30, 40). Theoretically, the different PRP concentrations in the trials might affect the study's primary endpoints. Furthermore, increasing the number of injections or adjusting the period between injections might result in greater improvements in IIEF-EF. In this review, we cannot delve further to conduct meta-regression or subgroup analysis according to different treatment protocols due to the unmet required number of available trials (18).

The exact mechanism of how PRP improves erectile function is not yet fully understood. However, several theories suggest platelets are crucial in coagulation and promoting wound healing following an injury (41). Platelets also contain various growth factors, such as FGF, PDGF, and VEGF. These growth factors, as catalysts of regenerative processes, play a critical role in the recruitment of stem cells, modulation of inflammatory responses, and stimulation of angiogenesis. These intricate functions are responsible for the regeneration and repair of tissues (42).

In general, our analysis demonstrates a significant short-term improvement of the erectile function in mild to moderate ED patients receiving intracavernosal PRP compared to placebo with minimal side effects. The evidence's overall certainty level ranged from low to moderate, indicating that more research is quite probable to sig-

nificantly influence our confidence in the effect estimate and will probably affect the estimate (23, 43).
Despite the demonstrated benefit of PRP, careful caution should be taken before implementing this treatment in daily practice, because the available trials had limited sample sizes, short follow-up durations, and heterogenous treatment protocols. Currently, the international guideline classify PRP as a novel erectile dysfunction treatment that should only be implemented in clinical trials (29). However, It is possible that in the near future, further clinical trials will shed light on the significance of PRP for ED. Longer-term follow-up trials are required to establish the long-term efficacy and safety of PRP, as well as a more detailed analysis of the dose and interval of PRP injection to determine the most optimal treatment protocol. Moreover, the benefit of combining PRP with other regenerative medicines might also be explored in future clinical trials.

Conclusions

Our findings highlights potential role of PRP as part of future ED treatment. Results from high-level evidence demonstrate a short term improvement of erectile function parameters up to 6 months in mild to moderate ED patients following intracavernosal injection of PRP. Future RCTs with longer duration follow-up and more standardized treatment protocols are necessary for gaining sufficient details on long-term effectiveness and safety of PRP.

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